Title: Efficacy of the Quell Wearable Device for Treatment of Central Sensitization-related Pain Among Persons with Chronic Overlapping Pain Conditions

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RESEARCH DESIGN AND METHODS

We will recruit 115 patients (see power analysis) with a presentation of multiple COPCs and randomize each of the subjects to one of two treatment conditions: 1) the standard Quell device, and 2) a Sham Quell device (control). All participants will be adults age 21 or older with multiple chronic pain conditions and QST-assessed evidence of sensory hypersensitivity. Patients will be invited to participate if they own a smartphone (iPhone or Android device) and can download the pain app and the Quell Relief mobile app onto their device. Individuals who are interested in the study and who do not own a smartphone will be supplied a temporary study-specific tablet to monitor their daily progress and to control their Quell device. Patients will be included if they (1) have chronic pain related to multiple chronic pain diagnoses (headaches, joint pain, back pain, or any of the other COPCs) for > 3 months' duration, (2) average 4 or greater on a pain intensity scale of 0 to 10, and (3) are able to speak and understand English. We will supply access to a Spanish version of the study pain app for those who are more comfortable responding in Spanish, but some English proficiency will be required. Subjects will need to meet the criteria outlined by Maixner and others (2016), for COPC to be considered for inclusion in this trial: (1) multiple pain sites and two or more pain diagnoses, (2) pain for 3 months or longer, (3) pain that is not accounted for by any other progressive disease (e.g., cancer, MS), and (4) meet hypersensitivity cutoffs based on QST (described below). (5) We will also require that the participants have a "physician diagnosis" of the pain conditions, meaning that they have been told that they have chronic overlapping pain conditions and their diagnoses have been entered in a medical record by a healthcare provider.

Patients will be excluded from participation if they meet any of the following criteria: (1) diagnosis of cancer or any other malignant disease, (2) acute osteomyelitis or acute bone disease, (3) present or past DSM-V diagnosis of schizophrenia, delusional disorder, psychotic disorder, or dissociative disorder that would be judged to interfere with study participation, (4) pregnancy, (5) any clinically unstable systemic illness judged to interfere with treatment, (6) a pain condition requiring urgent surgery, (7) an active substance use disorder, such as cocaine or IV heroin use (positive on the Mini International Neuropsychiatric Interview; M.I.N.I. v.5.0), that would interfere with study participation, and (8) have an implanted cardiac pacemaker, defibrillator, or other implanted device. All subjects will be asked to not change their treatment during the study period, (9) Raynaud's syndrome, or (10) Open cuts/sores.

Patients will be equally randomized to one of two experimental groups in this trial (i.e., Active Quell or Sham Quell) with the goal of having 50 subjects complete the trial in each group. The Sham Quell will look exactly like the Active Quell but will be programmed to give 2 minutes of stimulation three times during the 1-hour therapy session (2 minutes of stimulation at 0, 28, and 58 minutes, etc.). Subjects will be told that they will be exposed to two treatment conditions, lower intensity or higher intensity stimulation, and will be asked to use the device (standard or sham) every day for 12 weeks. Neither the investigators nor the study participants will know for sure which device they will be receiving. All subjects will complete assessment measures and be followed for 3 months. Recruitment will not be

restricted based on race or ethnicity. Efforts will be made to recruit at least 15% minorities. Since COPCs are identified more often among women than men, we will actively recruit at least 25% males. All participants will get assistance in downloading both the pain app and Quell Relief mobile app and have access to a research assistant (RA) who will answer any questions and help manage any problems that the individual may encounter. All participants will also be given a more extensive battery of QST testing at baseline and again at the end of the study. We will use an enriched design by first having the potential subjects try the Quell device. We anticipate that very few potential study participants will decide not to participate in a trial because they dislike the feeling of the Quell based on the results of previous trials. If they find that they would be willing to use the device they will be included in the study. If they dislike using the device on an initial trial, their age, gender, ethnicity and pain duration will be noted and the participants will be thanked for their interest in the study and dismissed.

All subjects (Quell and Sham Quell condition) will be encouraged to use their assigned device for at least 3 therapy sessions (3 hours of stimulation) every day, and to wear the device as often as possible, including while sleeping. Tracking of use of the device will be available electronically through the Quell Relief mobile app (subject data will be de-identified on the Quell server). All demographic and daily pain assessment data will be stored on a secure server (Mass General Brigham Amazon Web Server - MGB AWS) using the Veracode-tested study pain app and portal. Messages will be sent via the 2-way messaging pain app program to help track use of the device and to monitor and encourage active participation. Subjects will be instructed to enter daily assessments only when they are wearing the Quell device. Patients who wish to discontinue the study will be allowed to do so at their request. If the participant is willing, we will meet with her or him to understand reasons for discontinuing the study and problem-solve to see if there would be a way to keep following the individual. All subjects will be asked to complete a packet of questionnaires at the conclusion of the first 6-week study phase and then at the 3-month mark. All subjects will also be asked to participate in the full QST session described below at baseline, and then again at the end of the study (i.e., QST will be completed at the same post-study visit when outcome measures are collected). Each subject will be compensated $50 at baseline, $25 mid study, and $100 at study completion upon receipt of their completed questionnaires for a possible total of $175. At the end of the study subjects will be informed which device was the standard Quell device and they will be encouraged to keep this device for future use. Those in the Sham treatment arm will be offered a standard Quell for use after the study. It is expected that 15% of the subjects will dropout before completing the trial and recruitment of a total of 115 subjects may likely be needed to successfully complete the study.

Quantitative Sensory Testing (QST) Protocol: All subjects will be administered a battery of sensory assessment measures at baseline and again at the end of the 3-month study. A list of the QST measurements used in this proposed study is presented in Table 2. We will assess mechanical pain assessment and cold pain assessment. For mechanical pain, responses to punctate mechanical stimuli will be measured using a standard set of weighted probes (pinprick stimulators) that provides estimates of pain threshold and mechanical temporal summation. Singular taps will be performed on the metacarpophalangeal joint of the middle finger of the non-dominant hand using these probes *(Touch-Test Sensory Evaluator; www.ncmedical.com*) developed by the German Research Network (Backonja, 2009). The lowest-force stimulator that produces a sensation of discomfort at the level 10 out of a 100-point scale will then be used to assess the temporal summation of pain that occurs with rapid administration of identical stimuli for a series of 10 pinpricks (with 1-second inter-stimulus intervals). Participants will be asked to rate the painfulness of the first, fifth, and tenth stimulus; mechanical temporal summation will be defined as the increase in pain from the first to the final stimulus. A Somedic pressure algometer will be utilized to assess responses to pressure stimulation at several

anatomical sites. Pain pressure thresholds (PPT) will be determined twice on the right and left sides of the body: the trapezius, and thumb joint. Mechanical pressure will be applied using a 0.5-cm^2 probe covered with 1mm polypropylene pressure-transducing material; pressure will be increased at a steady rate of 30 kPA/s until the subject indicates that the pressure is painful. Finally, we will use cuff algometry to assess responses to sustained mechanical pressure. A Hokanson rapid cuff inflator will be used to inflate a standard blood pressure cuff around the gastrocnemius muscle of the dominant leg until the subject indicates a pain level was 40 out of a 100-point scale. This pressure will be used in the next test and will not be changed. Over the course of 2 minutes, at 30 second intervals, the subject will be asked to rate her or his current pain level on a scale 0 to 100. As with each of these psychophysical testing procedures, participants will be informed that they could terminate the procedure at any time.

For cold pain assessment, responses to noxious cold will be evaluated using a repeated cold pressor task (CPT), which involves immersion of the right hand in a circulating water bath (Neslab RTE17) maintained at a temperature of 4°C. The CPT is the most commonly used method of pain induction in the laboratory and has demonstrated clinical relevance. Participants will undergo a series of several cold pressor tasks, with the first 2 consisting of serial immersions of the dominant hand for 15 seconds, with 2 minutes between immersions. Once the subject removes their hand, pain ratings will be asked at 0 seconds, 15 seconds, 30 seconds, and 60 seconds. If the subject is not able to remain in the water for the full 15 seconds, they will be able to remove it at their discretion with the same post-water intervals. Conditioned Pain Modulation (CPM, which refers to the phenomenon of one noxious stimulus inhibiting the pain of a second noxious stimulus) will be measured during these cold pressor trials by assessing PPTh during the immersion. The final CPT will involve an immersion of the dominant hand lasting until a participant reached maximum pain tolerance (or a 3 min maximum). Their pain level will be asked in 15 second intervals while submerged and as soon as they removed the hand from the water. The participants will rate the intensity of the cold pain on a 0-100 scale ("no pain" to "most intense pain imaginable"). These procedures are similar to those we have utilized in prior studies of patients with OA and other chronic pain conditions (Jamison, 2018, 2019; Edwards, Wasan, 2011; Edwards, 2016). After 30% of the proposed sample has been enrolled, a blinded observer will assess the QST screening data to ensure that the proposed cutoffs are not excluding a problematically high percentage of interested participants.

Blinding: The proposed randomization ratio will be 1:1 Active to Sham device. The Sham device is identical to the Active Quell in all aspects with one exception. While the Active Quell typically delivers 1 hour of continuous stimulation during a therapy session, the Sham Quell device will deliver only three 2-minute periods of stimulation (at 0, 28 and 58 minutes) within each 60-minute therapeutic session. Recent studies suggests that this limited stimulation offers some perceived analgesic effect (Jamison, Edwards et al., 2021; Jamison, Curran et al., 2021). The subjects will be informed that they will be receiving either low or high intensity therapy. Neither the principal investigator, the co-investigators, the research assistant (RA, who will serve as the study coordinator), nor the subjects will know if they are given a sham device or the actual Quell device. The devices will be randomly numbered and provided by NeuroMetrix and information about the device assignment will be managed through NeuroMetrix. At the end of 6 weeks and again after 3 months, subjects will be asked if they thought they had the Sham (low intensity) Quell or (high intensity) Active Quell device. The co-principal investigators and the RA will be asked to identify which subjects they thought had Active Quell vs the Sham Quell device prior to analyses of the data. Both the Active Quell and the Sham Quell will communicate via Bluetooth with the same mobile application. This application provides the subjects with a dashboard of device information, trending data on device usage, and sleep quality. This same information will be synced to a cloud database so that investigators involved in the study can collect these data remotely, as well as monitor

adherence with the device. In a past unpublished investigation when this blinding procedure was used among 17 subjects and 11 physicians, investigators accurately guessed the device (sham or active) a subject was randomized to in 11 of 17 participants (64.7%). Eleven of 17 (64.7%) study participants accurately guessed the device to which they were randomized. However, in a recent randomized study in which subjects were assigned to either an Active or Sham Quell device, most of the subjects (84.9%) believed that they had been assigned to the Sham Quell device (Jamison, Edwards et al., 2021; Jamison, Curran et al., 2021).

Patient Measures: Participants will complete measures recommended by the Initiative on Methods, Measures, and Pain Assessment in Clinical Trials (IMMPACT; Dworkin et al, 2005; Gewandter et al., 2021) as primary outcomes. We will be tracking the patients using validated measures of pain (The Brief Pain Inventory - BPI), coping (Pain Catastrophizing Scale - PCS), level of disability (Pain Disability Index - PDI), mood (Hospital Anxiety and Depression Scale - HADS), presence of neuropathic pain (Pain Detect Neuropathic Pain Questionnaire - painDETECT), pain symptoms and function (Symptom Impact Questionnaire - SIQR), impression of change (Patients' Global Impression of Change - PGIC), healthcare utilization (monthly clinic and ED visits), and overall satisfaction (Satisfaction and qualitative questions developed for this study specifically related to use of a pain management device; see Table 1). We will also track daily ratings of pain, sleep, activity interference, and mood through the pain app. Objective measures of activity, gait, and sleep will be collected by the devices. The 7-item activity interference scale of the Brief Pain Inventory will serve as the primary outcome.

Research Objectives: This study is expected to take 18-24 months to complete and is designed to gather information about the use of the Quell for persons with COPCs. We hypothesize that those using the Active Quell device will report reduced pain compared with the Sham Quell condition. We also expect that those using the active device will show improvement in sleep, mood, and level of activity over the 3-months of using the device. We hypothesize that frequency of using the Quell (increased tolerability and adherence) will be correlated with greater reduction in pain. We hypothesize that the device will be safe to use and will demonstrate a reduction in healthcare utilization (reduced clinic and ED visits). We will also investigate use of prescription opioids and other nonopioid pain medications among the study subjects and determine the effect of daily use of the Active Quell (vs. Sham Quell) on intake of prescription pain medication. Finally, based on preliminary analyses from prior Quell studies, we will investigate whether certain individuals report greater benefit from using the Active Quell than others and, in particular, we predict that those with more pain sensitivity and longer duration of pain will demonstrate most benefit from the Active Quell. The previous studies in LBP and fibromyalgia patients both yielded evidence that the most pain-sensitive patients reported the greatest reductions in pain with Active Quell use. In the present proposal, we will be recruiting participants with evidence of sensitization at baseline and we will evaluate whether the most-sensitized patients with COPCs, even within a generally sensitized group of patients, show the greatest analgesic benefits. We will examine trends from the daily pain ratings on the pain app since it gives multiple daily pain ratings over the course of the study. We will target the 7-item activity interference subscale of the BPI (0=does not interfere; 10=completely interferes) as the primary outcome, and the PCS, PDI, HADS, painDETECT, SIQR, PGIC, healthcare utilization, and satisfaction questions as secondary outcome measures.

Statistical POW

Power calculations, as outlined by Cohen (1988), were performed to determine the probability of detecting clinically significant differences between treatment conditions in the primary area of measurement. These calculations assumed a two-tailed test and alpha level of 0.05 confirming the

hypotheses that the Active Quell would be associated with general overall improvement in activity interference on the activity subscale of the Brief Pain Inventory. In our previous work (Jamison, Wan et al., 2019; Jamison, Curran et al., 2021; Jamison, Edwards et al., 2021), we had a high rate of consent to participate among recruited patients, with minimal attrition. We assessed power based on our preliminary data and previously published studies. The power analysis revealed that a sample size of 100 subjects (50 per treatment arm) using a 2-sample t-test for a difference in mean pre/post change score gives the study a >85% probability of detecting a 1.5-point group difference on a 0-10 rating scale (assuming a standard deviation of 1.8). Conventional metrics suggest that a 30% change or difference score is clinically meaningful (Dworkin et al., 2021), and this sample size would provide adequate power to detect a group difference of approximately 20%. Most of the analyses in the proposed study will involve delta scores reflecting changes within subjects (both uncorrected and adjusted - least squares, LS). We also will conduct multi-level modeling analyses of the daily pain assessments. We will examine the distribution of the delta scores between treatment arms and will ascertain whether that distribution is normal. This information will allow us to determine whether parametric (e.g., ANCOVA) or nonparametric analyses should be used. Collectively, this sample size (n=100 total), together with our previously observed very high retention rates and the substantial efficacy of the device, will provide more than adequate power to detect moderate-size effects.

Multivariate imputation with chained equations (MICE) will be used to fill in missing assessments (including for subjects that drop out). MICE is valid under the assumption that data is missing at random (MAR). Variables will be modeled using normal regression. For each efficacy measure, the imputation model will include the available baseline, week-6 and 3-month data, demographics (age, BMI, education) and pain characteristics. The active and sham groups will be separately imputed. The same random-number seed will be used for computation of 250 complete (i.e., no missing data) datasets for each efficacy measure. For each dataset, the 3-month least-square mean change scores will be determined. The results will then be combined according to Rubin's rule. A sensitivity analysis for data missing not at random (MNAR) rather than MAR will be performed using delta-based MI. Specifically, the LS mean change scores will be reanalyzed with deterministic increases to the 3-month assessments (i.e., smaller change scores) of subjects on active treatment that withdrew from the study.